

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/763,377                      Confirmation No. 7571  
Appellant : Yat Sun Or  
Filed : January 23, 2004  
TC/A.U. : 1623                      Examiner : Ganapathy Krishnan  
Docket No. : 4014.1074 US

For: Bridged Macrocyclic Compounds and Processes for the Preparation Thereof

REPLY BRIEF

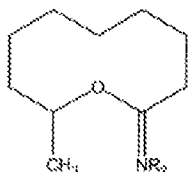
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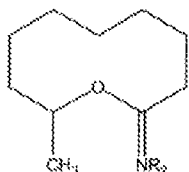
Sir:

This Reply Brief is being filed pursuant 37 CFR 41.41 in response to the Examiner's Answer mailed October 09, 2007. The Appeal Brief filed on July 26, 2007 is incorporated herein by reference.

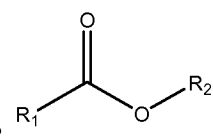
Rejection of Claim 1 under 35 USC 112, first paragraph

The Examiner has maintained the rejection of independent claim 1 under 35 U.S.C. 112, first paragraph, asserting that while the specification is enabling for macrolides, it does not reasonably provide enablement for a process using any macrocyclic compound. The Examiner further stated in the Examiner's answer on page 6 that the oxygen and NR<sub>2</sub>



in  are nucleophilic since the oxygen and the nitrogen atoms both have lone pair of electrons. The Examiner asserted that such macrocycle cannot form a bridge as instantly claimed. The Examiner concludes that since at least one macrocyclic compound could be envisioned that would not bridge, the specification is not enabling for its scope.

It is undisputed that the structure presented by the Examiner cannot form a bridge. However, a person having skill in the art would recognize that the oxygen in the above structure is not nucleophilic. While it is true that a nucleophile can have lone pair electrons; however the lone pair electrons must be available to attack an electrophile in order to act as a nucleophile. A nucleophile requires more than just the mere existence of

lone pair. For example, esters such as, , are not considered nucleophile even though the oxygen atoms contain lone pair electrons. In fact, esters are known as electrophiles.

Indeed, in this case, the Examiner selected this compound because he is confident it cannot undergo a bridging reaction. The identification of what is apparently an obvious compound that will fail in the reaction does not prove that the rejection is proper. Further, in cases where it is hard to predict the bridge formation, it would only be routine experimentation for one of ordinary skill in the art to carry out the process as instantly claimed and determine which macrocycles would be inoperative or operative. The Appellant submits that the process as instantly claimed has been exemplified on a variety of complex macrolide structures and the specification provides ample directions and

guidance to carry out the process. A skilled person in the art can easily determine which embodiments would be inoperative or operative following the instant claimed process without undue experimentation.

Furthermore, the presence of one or more “failed” experiments does not necessarily render a claim nonenabled. Indeed, in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), five out of nine embodiments made were inoperative. Yet the USPTO determined that the claims were enabling because the specification provides a considerable amount of direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to test the compounds were well known, and that there was a high level of skill in the art at the time the application was filed. *Wands* does not require that the outcome of each experiment be successful or predicted a priori. The Appellant submits that the teaching in the present specification establishes that it does not take undue experimentation to be successful.

The Examiner stated the seven Wand factors asserting that the terms macrocyclic compound and catalyst are broad. The Appellant respectfully disagrees. While it is true that not all macrocyclic compounds can achieve a bridged macrocyclic, that fact alone does not support a finding that the application lacks enablement. It is believed that the Appellant has provided sufficient guidance for a skill artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties and determine whether the process was successful and those conditions that are appropriate for carrying out the process without undue experimentation.

#### **The breadth of the claims**

The Examiner states that the “term macrocyclic compound and catalyst are broad and are seen to encompass several macrocyclic compounds other than macrolides recited in the instant claim 5.” It is agreed by the Examiner that the Appellant has enabled the process of the invention with respect to macrolides characterized by at least two nucleophilic moieties. It is believed that such a process can be successfully applied to other macrocyclic systems characterized by at least two nucleophilic moieties. While it is recognized that not all macrocyclic systems can successfully achieve a bridged macrocyclic using the described process, this fact alone does not support the rejection. The Appellant has provided sufficient guidance in the specification for a skill artisan to apply the process

of the invention to any macrocyclic characterized by at least two nucleophilic moieties and determine whether the process will be successful. In addition, the terms “macrocyclic compound” and “catalyst” are commonly used in the art of chemistry. A skilled chemist can readily determine those macrocyclics “characterized by at least two nucleophilic moieties” and catalysts which will be successful.

**The state of the prior art**

The Examiner presented a random structure in the office action and states that both the oxygen and the nitrogen in the structure with their electron pairs are seen as nucleophilic moieties and that such compound cannot form a bridge with a bridging component as instantly claimed. The Appellant respectfully disagrees. It is assumed that the structure as drawn denotes  $R_2$  as a variable rather than two R groups, to achieve a nucleophilic nitrogen. While it is true that the oxygen atom contains unpaired electrons, it is not considered nucleophilic because the unpaired electrons are delocalized to the imine double bond. Nucleophilicity is not simply defined by the existence of unpaired electrons. Even if it were true that a skilled artisan would consider this compound to be a macrocycle substituted by two nucleophilic moieties and assuming that it were true that the compound (which is likely to be unstable) would not undergo the reaction described in the claim, that fact does not support the rejection. Firstly, it is not seen that the claimed process embraces a process where no bridging reaction occurs. Secondly, it would not require undue experimentation to confirm whether or not a reaction would occur using this compound. Because the function of the claim is to not (1) to define the starting materials to only those compounds where successful reaction is a certainty or (2) to preclude any starting material that is not or will not be successful, the fact that the Examiner can identify a compound which, in his opinion, is unlikely to react does not support the rejection.

**The level of predictability in the art**

The Examiner states that there is insufficient data to substantiate that a bridged product as instantly claimed can be made with any macrocyclic compound comprising two nucleophilic moieties. The Appellant respectfully disagrees. It is believed that the Examiner has agreed that the enablement for the process of the invention to macrolide systems characterized by at least two nucleophilic moieties has been met by the Appellant. Macrolide systems are more complex than most macrocyclic systems with two nucleophilic

moieties. Therefore, the success of such complex systems allows for predictability of other macrocyclic systems characterized by two nucleophilic moieties as well. The Appellant has provided sufficient guidance for a skill artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties and determine whether the reaction will be successful. The law does not require the Appellant to ensure that the claims are drafted to ensure that the description of the starting materials explicitly preclude those starting materials which will not be successful. No more is required.

**The amount of direction provided by the inventor**

The Examiner states that the instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the formation of a bridged product as instantly claimed using any macrocyclic compound comprising two nucleophilic moieties. The Appellant respectfully disagrees. Since the enablement for complex macrolide systems has been met, there is no reason to conclude that the instant specification does not provide enough guidance. As stated above, the Appellant has provided sufficient guidance for a skill artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties. No more is required.

**The existence of working examples**

The Examiner states that the working examples set forth in the instant specification are drawn to formation of a bridged product using erythromycin as the macrocyclic compound and that there is little enabling disclosure for the same process to be extended to any macrocyclic compound. The Appellant respectfully disagrees. The amount of guidance provided in the application is sufficient for anyone skilled in the art to determine which embodiment that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. The existence of working examples using erythromycin as the macrocyclic compound provides plenty of guidance for a skilled artisan to apply the said process to any macrocyclic compounds without undue experimentation. Indeed, this kind of guidance is typical in the art as can be seen by reviewing any standard chemistry textbook.

**The quantity of experimentation needed to make or use the invention based on the content of the disclosure**

The Examiner states that the instant disclosure is not seen to be sufficient to enable the use of any macrocyclic compounds in the process as instantly claimed and that one of ordinary skilled in the art would have carry out the process in order to determine the type of macrocyclic compound and the type of nucleophilic moiety and the type of catalyst needed to carry out the said process. The Appellant respectfully disagrees. While it is true that one of ordinary skilled in the art would have to carry out the process in order to confirm which macrocyclic systems will be successful, it would not require undue amount of experimentation to do so. Indeed, the likelihood of success in many instances will be predictable where, for example, highly unstable starting materials are employed. As explained in MPEP 2164.08, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious. *In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970). It is respectfully submitted that such guidance that need not be included are teachings that refer to starting material instability and the like. The guidance as to “how to use” the claimed process is set forth in the application and there is expenditure of no more effort than is normally required in the art to carry out such process.

As the claims only embrace processes which achieve a bridged macrocyclic product, it is not believed that the claims embrace any inoperative embodiments. However, even if the Examiner were to disagree with this position, the specification is still enabling because undue experimentation is not involved in determining those processes that are successful and operative. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). The Appellant respectfully requests that all rejections under 35 U.S.C. §112, first paragraph be reversed.

Rejection of Claims 1-12 under 35 USC 103(a)

The Examiner has maintained the rejection under 35 U.S.C 103(a) of independent claims 1-12 as being obvious over PCT Application WO99/21864 (“WO ‘864”).

The rejection notes that WO '864 teaches a process for making a bridged macrocyclic compound with the bridging components  $\text{H}_2\text{N}-(\text{CH}_2)_m\text{-A-B-D-X}$  and  $(\text{CH}_2)_2\text{-C}=\text{CH}_2$ . The Examiner asserts that the macrocyclic compounds disclosed in WO'864 has at least two nucleophilic groups and are structurally very close to the macrocyclic compounds used for the said bridging in the instant process. The Examiner further states that the second bridging component with the double bond forms a pi-allyl complex with a metal. The Examiner admits that difference between the claimed and prior art processes is in that the prior art uses two bridging components to achieve a bridge while the claimed invention uses a single bridging component.

In the Examiner's answers, the Examiner asserts that the macrocycles and one of the bridging components disclosed by WO'864 meet the limitations of the instant claims. The Examiner further states that one of skill in the art will recognize that the same type of bridging can be achieved by having all the structural limitation of the bridging group in a single component and that the prior art need not to explicitly teach this. The Appellant respectfully disagrees. While it is true that the macrocycles and one of the bridging components disclosed by WO'864 fall into the definitions macrocyclic and bridging component of the presently claimed invention, the WO'864 disclosure as a whole do not meet all the limitations of claim 1. Claim 1 recites:

1. A process comprising the step of reacting a macrocyclic compound characterized by at least two nucleophilic moieties with a bifunctional bridging component characterized by its ability to form  $\pi$ -allyl metal complex in the presence of catalyst thereby achieving a bridged macrocyclic product.

The process comprising the step of reacting a macrocyclic compound characterized by at least two nucleophilic moieties with the second bridging component disclosed in WO'864 which contain a double bond capable of forming a pi-allyl metal complex do not meet the limitation of "thereby achieving a bridged macrocyclic product". The bridged macrocyclic product in the prior art process can not be formed following the process stated in claim 1. The bridged macrocyclic product in the prior art can only be achieved with further chemical modification(s). It is clear that the use of only the second component

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containing a double bond capable of forming a pi-allyl metal complex disclosed in WO'864 do not meet all the limitations of claim 1 of the present invention.

The Examiner statement regarding the fact the side reactions are possible in many organic reactions and that side reactions in general need not necessarily reduce the yield to such an extent that the process is not worth doing. The Appellant is not disputing this statement, however the suggestion of coupling the two individual bridging components disclosed in WO'864 before bridging onto the macrocyclic is unfeasible. The bridging components contain a total of four functional groups that will polymerize and gives complex mixture. It would be difficult to isolate the desired coupled product.

The Appellant asserts that the present process is unobvious in view of the discussion above. The Appellant respectfully requests that the rejections be reversed.

Respectfully submitted,

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